PRV

PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

Intyg
Certificate

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

Ansökan ingavs ursprungligen på engelska.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

The application was originally filed in English.

(71) *Sökande* *Astra AB, Södertälje SE*
Applicant (s)

(21) *Patentansökningsnummer* *9401928-8*
Patent application number

(86) *Ingivningsdatum* *1994-06-03*
Date of filing

Stockholm, 2005-10-14

För Patent- och registreringsverket
For the Patent- and Registration Office

Hördis Segerlund

Avgift
Fee *170:-*

PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

Metallic implant. 94-06-03

Technical field of the invention.

The present application relates to biocompatible metallic bone implants, preferably made of titanium or an alloy thereof, and to a method for treating metallic implants to enhance their biocompatibility.

Background to the invention.

A commonly used method for implanting metallic implants into bone tissue is a two stage procedure involving in a first operation surgically placing the implant into the bone tissue, where it is then allowed to rest unloaded and immobile for a healing period of three months or more in order to allow the bone tissue to grow onto the implant surface so as to permit the implant to be well attached to the bone tissue, the cut in the soft tissue covering the implant site being allowed to heal over the implant, and in a second operation opening the soft tissue covering the implant and attaching the functional parts to the implant. This two-stage procedure is often used in connection with dental implants, one reason being that it minimizes the risk of infection of the implant site from the oral cavity. In some orthopaedic applications the above two-stage surgery may not be necessary since most orthopaedic implants do not penetrate the soft tissue. A prolonged healing period is however still considered necessary since any movements of the implant in the weeks and months following surgery may endanger the final attachment of the implant to the bone tissue.

The above procedure is for instance described in

Brånemark et al: "Osseointegrated Implants in the Treatment of the Edentulous Jaw, Experience from a 10-year period", Almquist & Wiksell International, Stockholm - Sweden.

However, the fact that the implant may not be loaded means that the functional parts of the implant may not be attached to the implant and/or used during the healing period of three months or more. In view of the discomfort associated with this, it is desirable to minimize the time period necessary for the above-mentioned first stage and in some cases, for instance in certain orthopaedic applications, substantially dispense with said first stage and perform the entire implantation procedure in a single operation.

An object of the present invention is to provide an implant with improved rate of bone tissue attachment such that the post-surgery healing period described above may be reduced.

Some of the metals or alloys used for bone implants are capable of forming a strong bond with the bone tissue, a bond which may be as strong as the bone tissue per se, sometimes even stronger. The most notable example of this kind of metallic implant material is titanium and alloys of titanium whose properties in this respect have been known since about 1950. This bond with the bone tissue has been termed "osseointegration" by Brånemark et al.

Although this bond between titanium and bone tissue is comparatively strong, in some applications it is desirable to enhance the bond between metal and bone tissue. Earlier attempts to provide stronger bonds have involved the provision of a layer of hydroxy-apatite on

the surface of the metal, the rationale being the stimulation of tissue regeneration around the implant. The application of a separate coating of this kind may however involve the risk of flaking, i. e. although the bond between bone tissue and coating may be stronger than the normal bond between implant and bone tissue, the bond between implant and coating may actually be weaker than the normal bond between implant and bone tissue. A further object of the invention consequently is to provide an implant forming a stronger bond with the bone tissue. A still further object of the present invention is to provide a method for treating a metallic surgical implant in order to provide it with the properties mentioned above.

Short description of the inventive concept.

The above objects have been achieved by means of a metallic implant for implantation in bone tissue, the surface of said metallic implant containing fluorine and/or fluoride ions in an amount equal to that obtained by means of treatment of such implant with a 0.2% by volume aqueous solution of hydrofluoric acid at room temperature for 10 - 50 seconds (all percentages used below in connection with hydrofluoric acid solutions will be by volume), it surprisingly having been found that metallic implant surfaces having this flourine content will stimulate the growth of bone tissue in the vicinity of the implant surface as well as enhance the bond strength between implant and bone tissue.

One way of producing an implant according to the present invention is by means of a method for treating metallic implants comprising immersing the metallic implants into a 0.2% aqueous solution of hydrofluoric acid at 15 - 25°

C for a time period ranging from 10 to 50 seconds. The above objects are also achieved by means of a metallic implant having been treated by this method.

Preferred embodiments of the invention are set forth in the dependent claims.

Short description of the appended drawings

Fig 1 is a diagram illustrating the pushout force as well as the fluorine and oxygen content of an implant surface treated with 0.2% HF as a function of the treatment time.

Fig 2 is a SEM photograph of an implant surface treated with 0.2% HF for 30 seconds, in a magnification of 10 000 times,

Fig 3 is the implant surface in Fig 2, in 52 000 times magnification,

Fig 4 is a SEM photograph of an implant, in 10 000 times magnification, having been treated with 0.2% HF for 90 seconds,

Fig 5 is the surface of Fig 4 in 52 000 times magnification.

Fig 6 is a SEM photograph of an untreated implant surface in 52 000 times magnification.

Detailed description of the invention

The object of the invention is achieved by means of a metallic implant for implantation in bone tissue having a surface with a fluorine content in an amount equivalent

to that of a reference implant surface having been treated with an aqueous solution of hydrofluoric acid having a concentration of 0.2 percent by volume at room temperature for 10 - 50 seconds. Room temperature is normally considered to be about 21° C.

In a preferred embodiment the metallic implant for implantation into bone tissue is made of commercially pure titanium or of an alloy of titanium.

In another preferred embodiment the content of fluorine and/or flourine ions and the content of oxygen in the surface of the implant should be equivalent to the amount thereof in the reference implant surface.

In a third preferred embodiment the metallic implant for implantation in bone tissue should contain oxygen and/or fluorine (and/or fluoride ions) in an amount equivalent to that present in the reference implant surface after treatment with 0.2% aqueous solution of hydrofluoric acid at room temperature for 30 seconds.

The reference implant surface treated should be made of titanium grade 3, and should be made by turning at an average speed of about 7 meters per minute. No cutting fluid should be used. The cutting tool should be mde of high speed steel.

Before the treatment in the hydrofluoric solution, the reference implant surface is to be cleaned by a standard cleaning procedure involving the following steps:

1. Treatment with trichloroethylene with ultrasonic treatment for 15 minutes.

2. Rinsing in absolute ethanol for 10 seconds.

3. Three successive treatments with ethanol with ultrasonic treatment, each for 10 minutes. Each cleaned implant should then be sterile packaged in a Mediplast (TM) sterile envelope and autoclaved in a Citomat 162 (TM) (LIC Company) autoclave at 120 ^{o} C for 30 minutes.

Examples.

The result of an experiment in which the force necessary for removing (pushing out) substantially conical, unthreaded implants treated in 0.2% aqueous solution of hydrofluoric acid at room temperature for different time periods is illustrated in the diagram in Fig 1. The implants had been manufactured to have a diameter of 2 mm at one end, 3 mm at the other end and an overall length of 5 mm and were made from titanium grade 3 and cleaned and sterilized in accordance with the above procedures for treating the reference implant surface. The treatment times were 10 seconds, 30 seconds, 60 seconds, 90 seconds, 120 seconds and 180 seconds. Pushout tests were made and the pushout forces were marked in the diagram for each treatment time except 90 and 180 seconds. The content of flourine and of oxygen in the surface of the treated implants are also marked in the diagram for each treatment time. The values for an untreated control specimen are also given in the diagram as having a treatment time of 0 seconds. Each value for the pushout test results are a mean of the values for four implants implanted in the tibia of a respective rabbit and left to heal into the bone tissue for two months.

An Instron model 1121 tensile testing machine (Instron, U.K.) inter alia comprising a support jig and a ram

adjusted for a load range of 0 - 200 N, was employed to measure the force needed to separate each implant from bone. Milling tracks, to fit the support jig, were made in the specimen to be tested, in the bone surrounding the larger end of the implant, and the specimen was placed on the support jig. The ram was lowered at a speed of 1 mm/min and the maximum force required to separate the implant from the bone was measured.

The contents of fluorine and oxygen were measured by means of an Electron microprobe (CAMECA camebax) at SINTEF/SI in Oslo. The results as measured with this equipment were

	F%	O%
0 sec	0.01	5.1
10 sec	0.15	5.5
30 sec	0.11	5.8
60 sec	0.17	5.7
90 sec	0.2	9.4
120 sec	0.23	8.4
180 sec	0.16	11.0

The diagram clearly illustrates the higher values for the pushout tests resulting from treatment times varying between 10 and 50 seconds with a peak value at 30 seconds. The values for the remaining treatment times and the untreated control specimens are lower although the treated implants generally have higher values than the untreated ones. The values for the oxygen (5.5 to 5.8%) and fluorine content (0.11 to about 0.15%) of the surface of the implants for the treatment times between 10 and 50 seconds are lower than the corresponding values for the other treatment times.

There consequently seems to be a correlation between

content of fluorine and oxygen content of the implant surface and the strength of the bond between the implant surface and the bone tissue.

The pushout tests were made after a time period which was as short as two months. The rapid increase of the strength of the bond results in that the healing period necessary for reaching a given strength of the bone is shortened. The use of the treatment according to the invention thus facilitates the use of one-stage surgical procedures, particularly in orthopaedics, since the time the patient must remain inactive is shortened.

Fig 3 illustrates how the implant surface seems to be largely unaffected by the treatment according to the invention, no effect being discernable in a magnification of 10 000 times (the original tooling marks not being affected at all). This photograph should be compared with the photograph in Fig 5, in 10 000 times magnification, showing a surface which has been treated longer (90 seconds) than envisaged by the present invention and in which the marked change in the surface by the treatment in question is illustrated.

Fig 4, which shows the surface in Fig 3 in a magnification of 52 000 times, should be compared with Fig 7, which shows an untreated surface in a magnification of 52 000 times, and with Fig 6, which shows the surface of Fig 5 in a magnification of 52 000 times. As is evident, the surface treated according to the invention is only slightly affected, the tooling marks still being discernable, whereas the surface treated for a longer period of time is distinctly altered and covered with a porous layer.

In the above test implants manufactured and treated in the same way as the reference implant surface were used. It should however be noted that the metallic implants to be used in the clinical situation and/or in research of course can be manufactured of any metal and treated in any way within the scope of the claims provided the implant surface is equivalent to the reference surface in regard of the content of fluorine and oxygen.

The invention also relates to a method for treating metallic implants prior to implantation comprising the steps of

- cleaning and sterilizing the implant according to a standard procedure involving solvents and ultrasound,
- immersing the implants in a 0.2% aqueous solution of hydrofluoric acid at a temperature of 15 - 25° C for a time period of 10 - 50 seconds,

- rinsing said implant in an appropriate medium, preferably distilled water.

In a preferred embodiment of the method, the time period for treating the implant is 30 seconds, and in another preferred embodiment the treatment is performed at a temperature of 21° C.

The invention also relates to a metallic implant treated in accordance with this method.

The invention also relates to the use of a 0.2% aqueous solution of hydrofluoric acid for 10 - 50 seconds at room temperature to treat a metallic implant to improve the implant characteristics.

CLAIMS

1. Metallic implant for implantation in bone tissue, c h a r a c t e r i z e d in that the surface of said metallic implant contains fluorine and/or fluoride ions in an amount equivalent to that obtained by means of treatment of a reference implant surface with a 0.2% aqueous solution of hydrofluoric acid at room temperature for 10 - 50 seconds.

2. Metallic implant according to claim 1, c h a r a c t e r i z e d in that said metallic implant is made of commercially pure titanium or an alloy of titanium.

3. Metallic implant according to claim 2, c h a r a c t e r i z e d in that the surface of said metallic implants contains fluorine and/or fluoride ions in an amount equivalent to that obtained by means of a treatment with a 0.2% aqueous solution of hydrofluoric acid at room temperature for 30 seconds.

4. Metallic implant according to claim 2, c h a r a c t e r i z e d in that said surface contains flourine and oxygen in an amount equivalent to that present after treatment with a 0.2% aqueous solution of hydrofluoric acid at room temperature for 10 - 50 seconds.

5. Metallic implant according to claim 4, c h a r a c t e r i z e d in that said surface contains flourine and oxygen in an amount equivalent to that present after treatment with a 0.2% aqueous solution of hydrofluoric acid at room temperature for 30 seconds.

6. Method of treating metallic implants prior to implantation comprising the steps of

- cleaning and sterilizing the implant according to a standard procedure involving solvents and ultrasound,
- immersing the implants in a 0.2% aqueous solution of hydrofluoric acid at a temperature of 15 - 25° C for a time period of 10 - 50 seconds,

- rinsing said implant in an appropriate medium, preferably distilled water.

7. Method according to claim 6, c h a r a c t e r i z e d in that said time period is 30 seconds.

8. Method according to claim 6, c h a r a c t e r i z e d in that said treatment is carried out at 21° C.

9. Method according to claim 7, c h a r a c t e r i z e d in that said treatment is carried out at 21° C.

10. Metallic implant for implantation in bone tissue, c h a r a c t e r i z e d in that said implant has been treated with the method according to any one of claims 6 - 9.

11. Metallic implant for implantation into bone tissue, obtainable by treatment with a 0.2% aqueous solution of hydrofluoric acid at room temperature for 10 - 50 seconds.

12. Use of a 0.2% aqueous solution of hydrofluoric acid for 10 - 50 seconds at room temperature to treat a metallic implant to improve the implant characteristics.

13. Metallic implant for implantation in bone tissue, c h a r a c t e r i z e d in that the surface of the implant contains fluorine and/or fluorine ions to an amount of 0,11 to 0.15 % as measured with an Electron microprobe.

14. Metallic implant according to claim 13, c h a r a c t e r i z e d in that the surface of the implant contains oxygen to an amount of 5.5 - 5.8 % as measured with an Electron microprobe.

ABSTRACT

The present invention relates to a metallic implant for implantation in bone tissue having an increased rate of bone tissue attachment. The surface of said metallic implant contains fluorine and/or fluoride ions in an amount equal to that obtained by means of treatment of a reference implant surface with a 0.2% aqueous solution of hydrofluoric acid at room temperature for 10 - 50 seconds.

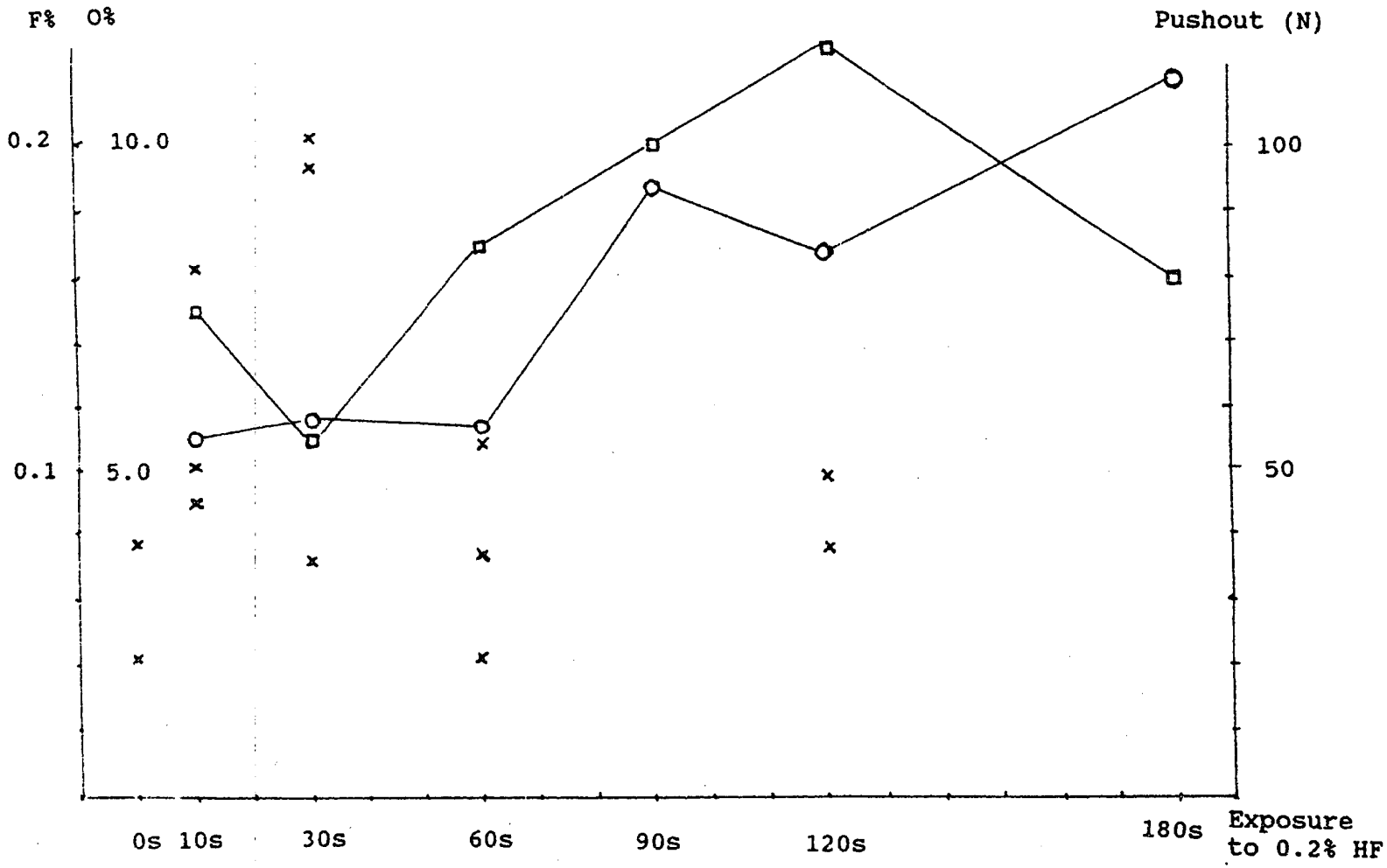

FIG 1. The relation between the concentration of F and O on the titanium surface and the biological effect as measured by push out technique.

FIG 2.

FIG 3.

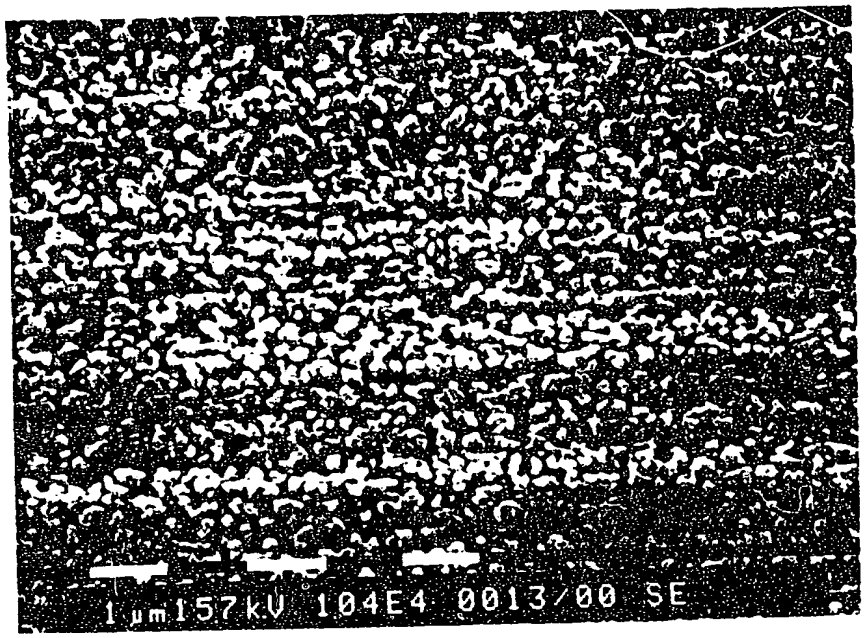

FIG 4.

FIG 5.

FIG 6.